A Genetic Analysis Package with R

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Contents

1 Introduction

This package was initiated to integrate some C/Fortran/SAS programs I have written or used over the years. As such, it would rather be a long-term project, but an immediate benefit would be something complementary to other packages currently available from CRAN, e.g. **genetics**, **hwde**, etc. I hope eventually this will be part of a bigger effort to fulfill most of the requirements foreseen by many, e.g. Guo and Lange (2000), within the portable environment of R for data management, analysis, graphics and object-oriented programming. My view has been outlined more formally in Zhao and Tan (2006a) and Zhao and Tan (2006b) in relation to other package systems. Also reported are Zhao (2005) and Zhao (2006) on package **kinship**.

The number of functions are quite limited and experimental, but I already feel the enormous advantage by shifting to R and would like sooner rather than later to share my work with others. I will not claim this work as exclusively done by me, but would like to invite others to join me and enlarge the collections and improve them.

2 Implementation

The following list shows the data and functions currently available.

* ANALYSIS *

AE3	AE model using nuclear family trios
bt	Bradley-Terry model for contingency table
ccsize	Power and sample size for case-cohort design
fbsize	Sample size for family-based linkage and association design
gc.em	Gene counting for haplotype analysis
gcontrol	genomic control
gcontrol2	genomic control based on p values
gcp	Permutation tests using GENECOUNTING
genecounting	Gene counting for haplotype analysis
gif	Kinship coefficient and genetic index of familiality
grmMCMC	Mixed modeling with genetic relationship matrices
hap	Haplotype reconstruction
hap.em	Gene counting for haplotype analysis
hap.score	Score statistics for association of traits with haplotypes
htr	Haplotype trend regression
hwe	Hardy-Weinberg equilibrium test for a multiallelic marker
hwe.cc	A likelihood ratio test of population Hardy-Weinberg equilibrium
hwe.hardy	Hardy-Weinberg equilibrium test using MCMC
kin.morgan	kinship matrix for simple pedigree
LD22	LD statistics for two diallelic markers
LDkl	LD statistics for two multiallelic markers
masize	Sample size calculation for mediation analysis
mia	multiple imputation analysis for hap
mtdt	Transmission/disequilibrium test of a multiallelic marker
mtdt2	Transmission/disequilibrium test of a multiallelic marker by Bradley-Terry model
mvmeta	Multivariate meta-analysis based on generalized least squares
pbsize	Power for population-based association design
pbsize2	Power for case-control association design
pfc	Probability of familial clustering of disease
pfc.sim	Probability of familial clustering of disease
pgc	Preparing weight for GENECOUNTING
print.hap.score	Print a hap.score object
s2k	Statistics for 2 by K table
tscc	Power calculation for two-stage case-control design

* GRAPHICS *

asplot	Regional association plot
ESplot	Effect-size plot
mhtplot	Manhattan plot
mhtplot2	Manhattan plot with annotations
pedtodot	Converting pedigree(s) to dot file(s)
plot.hap.score	Plot haplotype frequencies versus haplotype score statistics
qqfun	Quantile-comparison plots
qqunif	Q-Q plot for uniformly distributed random variable

* DATASETS *

PD	A study of Parkinson's disease and APOE, LRRK2, SNCA makers
aldh2	ALDH2 markers and alcoholism
apoeapoc	APOE/APOC1 markers and schizophrenia
cf	Cystic Fibrosis data
crohn	Crohn's disease data
fa	Friedreich ataxia data
fsnps	A case-control data involving four SNPs with missing genotype
hla	HLA markers and schizophrenia
l51	An example pedigree data
lukas	An example pedigree
mao	A study of Parkinson's disease and MAO gene
meyer	A pedigree data on 282 animals deriving from two generations
nep499	A study of Alzheimer's disease with eight SNPs and APOE

* UTILITIES *

SNP	Functions for single nucleotide polymorphisms (SNPs)
BFDP	Bayesian false-discovery probability
FPRP	False-positive report probability
ab	Test/Power calculation for mediating effect
b2r	Obtain correlation coefficients and their variance-covariances
chow.test	Chow's test for heterogeneity in two regressions
comp.score	score statistics for testing genetic linkage of quantitative trait
h2	Heritability estimation according to twin correlations for case-control studies
klem	Haplotype frequency estimation based on a genotype table of two multiallelic markers
makeped	A function to prepare pedigrees in post-MAKEPED format
metap	Meta-analysis of p values
metareg	Fixed and random effects model for meta-analysis
muvar	Means and variances under 1- and 2- locus (diallelic) QTL model
read.ms.output	A utility function to read ms output
twinan90	Classic twin models
whscore	Whittemore-Halpern scores for allele-sharing
GRM functions	ReadGRM, ReadGRMBin, ReadGRMPLINK, ReadGRMPCA, WriteGRM, WriteG handle genomic relationship matrix involving other software
heritability functions	h2G, VR, h2GC, h2l give point estimates as with their variances for continuous traits and binary traits under liability threshold model and case-control sampling

Assuming proper installation, you will be able to obtain the list by typing `library(help=gap)` or view the list within a web browser via `help.start()`. Assuming that you have already loaded the package via `library(gap)`, you can use `lsf.str("package:gap")` and `data(package="gap")` to generate a list of functions and a list of datasets, respectvely. If this looks odd to you, you might try `search()` within `R` to examine what is available in your environment before issuing the `lsf.str` command.

```
> library(gap)
> search()

 [1] ".GlobalEnv"        "package:gap"       "package:stats"
 [4] "package:graphics"  "package:grDevices" "package:utils"
 [7] "package:datasets"  "package:methods"   "Autoloads"
[10] "package:base"

> lsf.str("package:gap")

a2g : function (a1, a2)
ab : function (type = "power", n = 25000, a = 0.15, sa = 0.01, b = log(1.19),
    sb = 0.01, alpha = 0.05, fold = 1)
```

```
AE3 : function (model, random, data, seed = 1234, n.sim = 50000, verbose = TRUE)
allele.recode : function (a1, a2, miss.val = NA)
asplot : function (locus, map, genes, flanking = 1000, best.pval = NULL, sf = c(4,
    4), logpmax = 10, pch = 21)
b2r : function (b, s, rho, n)
BFDP : function (a, b, pi1, W, logscale = FALSE)
bt : function (x)
ccsize : function (n, q, pD, p1, alpha, theta, power = NULL, verbose = FALSE)
chow.test : function (y1, x1, y2, x2, x = NULL)
comp.score : function (ibddata = "ibd_dist.out", phenotype = "pheno.dat", mean = 0,
    var = 1, h2 = 0.3)
cov.invlogit : function (logit.p1, logit.p2, cov.logit)
Cox.est : function (case, ctl, k0, initial)
Cox.T : function (parms, case, control, k)
DevH0dominant : function (parms, case, control, k)
DevH0dominant.est : function (case, ctl, k0, initial)
DevH0recessive : function (parms, case, control, k)
DevH0recessive.est : function (case, ctl, k0, initial)
DevHaGdominant : function (parms, case, control, k)
DevHaGdominant.est : function (case, ctl, k0, initial)
DevHaGrecessive : function (parms, case, control, k)
DevHaGrecessive.est : function (case, ctl, k0, initial)
ESplot : function (ESdat, SE = TRUE, logscale = TRUE, alpha = 0.05, xlim = c(-2,
    8), v = 1, ...)
fbsize : function (gamma, p, alpha = c(1e-04, 1e-08, 1e-08), beta = 0.2, debug = 0,
    error = 0)
FPRP : function (a, b, pi0, ORlist, logscale = FALSE)
g2a : function (g)
g2a.c : function (g)
gc.control : function (xdata = FALSE, convll = 1, handle.miss = 0, eps = 1e-06, tol = 1e-0
    maxit = 50, pl = 0.001, assignment = "assign.dat", verbose = T)
gc.em : function (data, locus.label = NA, converge.eps = 1e-06, maxiter = 500,
    handle.miss = 0, miss.val = 0, control = gc.control())
gcode : function (a1, a2)
gcontrol : function (data, zeta = 1000, kappa = 4, tau2 = 1, epsilon = 0.01, ngib = 500,
    burn = 50, idum = 2348)
gcontrol2 : function (p, col = palette()[4], lcol = palette()[2], ...)
gcp : function (y, cc, g, handle.miss = 1, miss.val = 0, n.sim = 0, locus.label = NULL,
    quietly = FALSE)
genecounting : function (data, weight = NULL, loci = NULL, control = gc.control())
geno.recode : function (geno, miss.val = 0)
getb1star : function (b1, b2, rho, sdx1 = 1, sdx2 = 1)
getPTE : function (b1, b2, rho, sdx1 = 1, sdx2 = 1)
gif : function (data, gifset)
grec2g : function (h, n, t)
h2 : function (mzDat = NULL, dzDat = NULL, rmz = NULL, rdz = NULL, nmz = NULL,
    ndz = NULL, selV = NULL)
```

```
h2G : function (V, VCOV, verbose = TRUE)
h2GE : function (V, VCOV, verbose = TRUE)
h2l : function (K = 0.05, P = 0.5, h2, se, verbose = TRUE)
hap : function (id, data, nloci, loci = rep(2, nloci), names = paste("loci",
    1:nloci, sep = ""), control = hap.control())
hap.control : function (mb = 0, pr = 0, po = 0.001, to = 0.001, th = 1, maxit = 100,
    n = 0, ss = 0, rs = 0, rp = 0, ro = 0, rv = 0, sd = 0, mm = 0, mi = 0,
    mc = 50, ds = 0.1, de = 0, q = 0, hapfile = "hap.out", assignfile = "assign.out")
HapDesign : function (HaploEM)
hap.em : function (id, data, locus.label = NA, converge.eps = 1e-06, maxiter = 500,
    miss.val = 0)
HapFreqSE : function (HaploEM)
hap.score : function (y, geno, trait.type = "gaussian", offset = NA, x.adj = NA, skip.hapl
    locus.label = NA, miss.val = 0, n.sim = 0, method = "gc", id = NA,
    handle.miss = 0, mloci = NA, sexid = NA)
hmht.control : function (data = NULL, colors = NULL, yoffset = 0.25, cex = 1.5, boxed = FA
htr : function (y, x, n.sim = 0)
hwe : function (data, data.type = "allele", yates.correct = FALSE, miss.val = 0)
hwe.cc : function (model, case, ctrl, k0, initial1, initial2)
hwe.hardy : function (a, alleles = 3, seed = 3000, sample = c(1000, 1000, 5000))
invlogit : function (x = 0)
k : function (r, N, adjust = TRUE)
KCC : function (model, GRR, p1, K)
kin.morgan : function (ped, verbose = FALSE)
klem : function (obs, k = 2, l = 2)
LD22 : function (h, n)
LDkl : function (n1 = 2, n2 = 2, h, n, optrho = 2, verbose = FALSE)
logit : function (p = 0.5)
m2plem : function (a1, a2)
makeped : function (pifile = "pedfile.pre", pofile = "pedfile.ped", auto.select = 1,
    with.loop = 0, loop.file = NA, auto.proband = 1, proband.file = NA)
masize : function (model, opts, alpha = 0.025, gamma = 0.2)
MCMCgrm : function (model, prior, data, GRM, eps = 0, n.thin = 10, n.burnin = 3000,
    n.iter = 13000, ...)
metap : function (data, N, verbose = "Y", prefixp = "p", prefixn = "n")
metareg : function (data, N, verbose = "Y", prefixb = "b", prefixse = "se")
mht.control : function (type = "p", usepos = FALSE, logscale = TRUE, base = 10, cutoffs =
    colors = NULL, labels = NULL, srt = 45, gap = NULL, cex = 0.4, yline = 3,
    xline = 3)
mhtplot : function (data, control = mht.control(), hcontrol = hmht.control(), ...)
mhtplot2 : function (data, control = mht.control(), hcontrol = hmht.control(), ...)
mia : function (hapfile = "hap.out", assfile = "assign.out", miafile = "mia.out",
    so = 0, ns = 0, mi = 0, allsnps = 0, sas = 0)
micombine : function (est, std.err, confidence = 0.95)
mtdt : function (x, n.sim = 0)
mtdt2 : function (x, verbose = TRUE, n.sim = NULL, ...)
muvar : function (n.loci = 1, y1 = c(0, 1, 1), y12 = c(1, 1, 1, 1, 1, 0, 0, 0,
```

```
    0), p1 = 0.99, p2 = 0.9)
mvmeta : function (b, V)
PARn : function (p, RRlist)
pbsize : function (kp, gamma = 4.5, p = 0.15, alpha = 5e-08, beta = 0.2)
pbsize2 : function (N, fc = 0.5, alpha = 0.05, gamma = 4.5, p = 0.15, kp = 0.1, model = "a
pedtodot : function (pedfile, makeped = FALSE, sink = TRUE, page = "B5", url = "http://www
    height = 0.5, width = 0.75, rotate = 0, dir = "none")
pfc : function (famdata, enum = 0)
pfc.sim : function (famdata, n.sim = 1e+06, n.loop = 1)
pgc : function (data, handle.miss = 1, is.genotype = 0, with.id = 0)
plem2m : function (a)
plot.hap.score : function (x, ...)
print.hap.score : function (x, ...)
qqfun : function (x, distribution = "norm", ylab = deparse(substitute(x)), xlab = paste(di
    "quantiles"), main = NULL, las = par("las"), envelope = 0.95, labels = FALSE,
    col = palette()[4], lcol = palette()[2], xlim = NULL, ylim = NULL,
    lwd = 1, pch = 1, bg = palette()[4], cex = 0.4, line = c("quartiles",
        "robust", "none"), ...)
qqunif : function (u, type = "unif", logscale = TRUE, base = 10, col = palette()[4],
    lcol = palette()[2], ci = FALSE, alpha = 0.05, ...)
ReadGRM : function (prefix = 51)
ReadGRMBin : function (prefix, AllN = FALSE, size = 4)
ReadGRMPCA : function (prefix)
ReadGRMPLINK : function (prefix, diag = 1)
read.ms.output : function (msout, is.file = TRUE, xpose = TRUE, verbose = TRUE, outfile =
    outfileonly = FALSE)
revhap : function (loci, hapid)
revhap.i : function (loci, hapid)
s2k : function (y1, y2)
se.exp : function (p, se.p)
se.invlogit : function (logit.p, se.logit)
snp.ES : function (beta, SE, N)
snp.HWE : function (g)
snp.PAR : function (RR, MAF, unit = 2)
solve_skol : function (rootfun, target, lo, hi, e)
toETDT : function (a)
tscc : function (model, GRR, p1, n1, n2, M, alpha.genome, pi.samples, pi.markers,
    K)
ungcode : function (g)
VR : function (v1, vv1, v2, vv2, c12)
whscore : function (allele, type)
WriteGRM : function (prefix = 51, id, N, GRM)
WriteGRMBin : function (prefix, grm, N, id, size = 4)
WriteGRMSAS : function (grmlist, outfile = "gwas")
x2 : function (p1, p2, n1, n2)
z : function (p1, p2, n1, n2, r)
```

```
> data(package="gap")$results
```

```
      Package LibPath                                Item
 [1,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "CDKNgenes (CDKN)"
 [2,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "CDKNlocus (CDKN)"
 [3,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "CDKNmap (CDKN)"
 [4,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "PD"
 [5,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "aldh2"
 [6,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "apoeapoc"
 [7,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "cf"
 [8,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "crohn"
 [9,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "fa"
[10,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "fsnps"
[11,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "hla"
[12,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "hr1420"
[13,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "l51"
[14,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "lukas"
[15,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "mao"
[16,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "meyer"
[17,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "mfblong"
[18,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "mhtdata"
[19,] "gap"   "/tmp/RtmpOvHrux/Rinst1f9d77041cac" "nep499"
      Title
 [1,] "Example data for association plot"
 [2,] "Example data for association plot"
 [3,] "Example data for association plot"
 [4,] "A study of Parkinson's disease and APOE, LRRK2, SNCA makers"
 [5,] "ALDH2 markers and Alcoholism"
 [6,] "APOE/APOC1 markers and Alzheimer's"
 [7,] "Cystic fibrosis data"
 [8,] "Crohn's disease data"
 [9,] "Friedreich Ataxia data"
[10,] "A case-control data involving four SNPs with missing genotype"
[11,] "The HLA data"
[12,] "An example data for Manhattan plot with annotation"
[13,] "An example pedigree data"
[14,] "An example pedigree"
[15,] "A study of Parkinson's disease and MAO gene"
[16,] "A pedigree data on 282 animals deriving from two generations"
[17,] "Example data for ACEnucfam"
[18,] "An example data for Manhattan plot"
[19,] "A study of Alzheimer's disease with eight SNPs and APOE"
```

A PDF version of this file can be viewed with command `vignette("gap",package="gap")`.

You can cut and paste examples at end of each function's documentation.

Both *genecounting* and *hap* are able to handle SNPs and multiallelic markers, with the former be flexible enough to include features such as X-linked data and the later being able to handle large number of SNPs. But they are unable to recode allele labels automatically, so functions *gc.em* and *hap.em* are in *haplo.em* format and used by a modified function *hap.score* in association testing.

It is notable that multilocus data are handled differently from that in **hwde** and elegant definitions of basic genetic data can be found in the **genetics** package.

Incidentally, I found my C mixed-radixed sorting routine as in Zhao and Sham (2003) is much faster than R's internal function.

With exceptions such as function *pfc* which is very computer-intensive, most functions in the package can easily be adapted for analysis of large datasets involving either SNPs or multiallelic markers. Some are utility functions, e.g. *muvar* and *whscore*, which will be part of the other analysis routines in the future.

The benefit with R compared to standalone programs is that for users, all functions have unified format. For developers, it is able to incorporate their C/C++ programs more easily and avoid repetitive work such as preparing own routines for matrix algebra and linear models. Further advantage can be taken from packages in **Bioconductor**, which are designed and written to deal with large number of genes.

3 Independent programs

To facilitate comparisons and individual preferences, I have made the source codes available for 2LD, EHPLUS, GENECOUNTING, HAP which have enjoyed great popularity ahead of the genomewide association studies (GWAS) therefore are likely to be more familiar than their R couunterparts in `gap`. However, you need to follow their instructions to compile for a particular computer system.

I have included ms code (which is required by `read.ms.output`) and .xls files to accompany *read.ms.output* and *FPRP* and *BFDP* functions as with a classic twin example for ACE model in **OpenMx**. The package is now available from CRAN and earlier it can be installed with command,

```
source('http://openmx.psyc.virginia.edu/getOpenMx.R')
```

For these models it is actually simpler to use facilities as in package **mets**, which I now suggest.

A final category is `twinan90`, which is now dropped from the package function list due to difficulty to keep up with the requirements by the `R` environment but nevertheless you will still be able to compile and use otherwise.

4 Demos

You can also try several simple examples via *demo*:

```
library(gap)
demo(gap)
```

5 Examples

I would like to highlight *pedtodot pbsize*, *fbsize* and *ccsize* functions used for pedigree drawing and power/sample calculations in a genome-wide asssociatoin study as reported in Zhao (2007).

5.1 Pedigree drawing

I have included the original file for the *R News* as well as put examples in separate vignettes. They can be accessed via `vignette("rnews",package="gap")` and `vignette("pedtodot", package="gap")`, respectively.

5.2 Kinship calculation

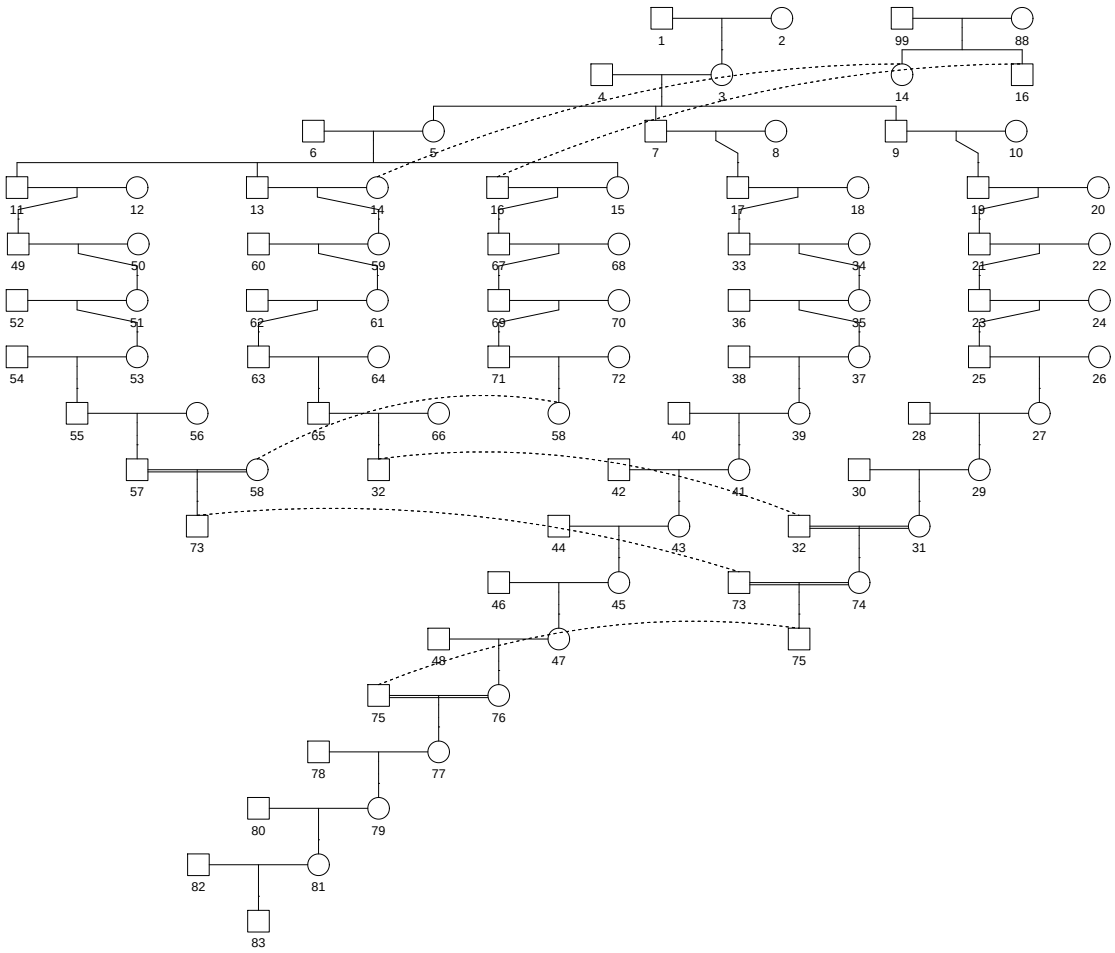
Next, I will provide an example for kinship calculation using *kin.morgan*. It is recommended that individuals in a pedigree are ordered so that parents always precede their children. In this regard, package **pedigree** can be used, and package **kinship2** can be used to produce pedigree diagram as with kinship matrix.

Pedigree diagram

```
> # pedigree diagram
> data(lukas,package="gap")
> library(kinship2)
> ped <- with(lukas,pedigree(id,father,mother,sex))
> pdf("figures/lukas.pdf",height=14,width=15)
> plot(ped)
> dev.off()

null device
          1
```

The pedigree diagram is as follows,



Kinship calculation

We then turn to the kinship calculation.

```
> # unordered individuals
> library(gap)
> gk1 <- kin.morgan(lukas)
> write.table(gk1$kin.matrix,"results/gap_1.txt",quote=FALSE)
> library(kinship2)
> kk1 <- kinship(lukas[,1],lukas[,2],lukas[,3])
> write.table(kk1,"results/kinship_1.txt",quote=FALSE)
> d <- gk1$kin.matrix-kk1
> sum(abs(d))

[1] 2.443634

> # order individuals so that parents precede their children
> library(pedigree)
```

```
> op <- orderPed(lukas)
> olukas <- lukas[order(op),]
> gk2 <- kin.morgan(olukas)
> write.table(olukas,"olukas.csv",quote=FALSE)
> write.table(gk2$kin.matrix,"results/gap_2.txt",quote=FALSE)
> kk2 <- kinship(olukas[,1],olukas[,2],olukas[,3])
> write.table(kk2,"results/kinship_2.txt",quote=FALSE)
> z <- gk2$kin.matrix-kk2
> sum(abs(z))

[1] 0
```

We see that in the second case, the result agrees with **kinship2**.

5.3 Study design

Family-based design

The example involving family-based design is as follows,

```
> library(gap)
> models <- matrix(c(
+          4.0, 0.01,
+          4.0, 0.10,
+          4.0, 0.50,
+          4.0, 0.80,
+          2.0, 0.01,
+          2.0, 0.10,
+          2.0, 0.50,
+          2.0, 0.80,
+          1.5, 0.01,
+          1.5, 0.10,
+          1.5, 0.50,
+          1.5, 0.80), ncol=2, byrow=TRUE)
> outfile <- "fbsize.txt"
> cat("gamma","p","Y","N_asp","P_A","H1","N_tdt","H2","N_asp/tdt","L_o","L_s\n",
+     file=outfile,sep="\t")
> for(i in 1:12) {
+     g <- models[i,1]
+     p <- models[i,2]
+     z <- fbsize(g,p)
+     cat(z$gamma,z$p,z$y,z$n1,z$pA,z$h1,z$n2,z$h2,z$n3,z$lambdao,z$lambdas,
+         file=outfile,append=TRUE,sep="\t")
+     cat("\n",file=outfile,append=TRUE)
+ }
> table1 <- read.table(outfile,header=TRUE,sep="\t")
> nc <- c(4,7,9)
> table1[,nc] <- ceiling(table1[,nc])
```

```
> dc <- c(3,5,6,8,10,11)
> table1[,dc] <- round(table1[,dc],2)
> unlink(outfile)
> # APOE-4, Scott WK, Pericak-Vance, MA & Haines JL
> # Genetic analysis of complex diseases 1327
> g <- 4.5
> p <- 0.15
> cat("\nAlzheimer's:\n\n")

Alzheimer's:

> fbsize(g,p)

$gamma
[1] 4.5

$p
[1] 0.15

$y
[1] 0.6256916

$n1
[1] 162.6246

$pA
[1] 0.8181818

$h1
[1] 0.4598361

$n2
[1] 108.994

$h2
[1] 0.6207625

$n3
[1] 39.97688

$lambdao
[1] 1.671594

$lambdas
[1] 1.784353

> table1
```

```
   gamma    p    Y   N_asp  P_A   H1 N_tdt   H2 N_asp.tdt  L_o  L_s
1    4.0 0.01 0.52    6402 0.80 0.05  1201 0.11       257 1.08 1.09
2    4.0 0.10 0.60     277 0.80 0.35   165 0.54        53 1.48 1.54
3    4.0 0.50 0.58     446 0.80 0.50   113 0.42        67 1.36 1.39
4    4.0 0.80 0.53    3024 0.80 0.24   244 0.16       177 1.12 1.13
5    2.0 0.01 0.50  445964 0.67 0.03  6371 0.04      2155 1.01 1.01
6    2.0 0.10 0.52    8087 0.67 0.25   761 0.32       290 1.07 1.08
7    2.0 0.50 0.53    3753 0.67 0.50   373 0.47       197 1.11 1.11
8    2.0 0.80 0.51   17909 0.67 0.27   701 0.22       431 1.05 1.05
9    1.5 0.01 0.50 6944779 0.60 0.02 21138 0.03      8508 1.00 1.00
10   1.5 0.10 0.51  101926 0.60 0.21  2427 0.25      1030 1.02 1.02
11   1.5 0.50 0.51   27048 0.60 0.50  1039 0.49       530 1.04 1.04
12   1.5 0.80 0.51  101926 0.60 0.29  1820 0.25      1030 1.02 1.02
```

Population-based design

The example involving population-based design is as follows,

```
> library(gap)
> kp <- c(0.01,0.05,0.10,0.2)
> models <- matrix(c(
+           4.0, 0.01,
+           4.0, 0.10,
+           4.0, 0.50,
+           4.0, 0.80,
+           2.0, 0.01,
+           2.0, 0.10,
+           2.0, 0.50,
+           2.0, 0.80,
+           1.5, 0.01,
+           1.5, 0.10,
+           1.5, 0.50,
+           1.5, 0.80), ncol=2, byrow=TRUE)
> outfile <- "pbsize.txt"
> cat("gamma","p","p1","p5","p10","p20\n",sep="\t",file=outfile)
> for(i in 1:dim(models)[1])
+ {
+    g <- models[i,1]
+    p <- models[i,2]
+    n <- vector()
+    for(k in kp) n <- c(n,ceiling(pbsize(k,g,p)))
+    cat(models[i,1:2],n,sep="\t",file=outfile,append=TRUE)
+    cat("\n",file=outfile,append=TRUE)
+ }
> table5 <- read.table(outfile,header=TRUE,sep="\t")
> table5
```

```
   gamma    p       p1     p5    p10   p20
1    4.0 0.01   46681   8959   4244  1887
2    4.0 0.10    8180   1570    744   331
3    4.0 0.50   10891   2091    991   441
4    4.0 0.80   31473   6041   2862  1272
5    2.0 0.01  403970  77530  36725 16323
6    2.0 0.10   52709  10116   4792  2130
7    2.0 0.50   35285   6772   3208  1426
8    2.0 0.80   79391  15237   7218  3208
9    1.5 0.01 1599920 307056 145448 64644
10   1.5 0.10  192105  36869  17465  7762
11   1.5 0.50   98013  18811   8911  3961
12   1.5 0.80  192105  36869  17465  7762
```

Case-cohort design

For case-cohort design, we obtain results for ARIC and EPIC studies.

```
> library(gap)
> # ARIC study
> outfile <- "aric.txt"
> n <- 15792
> pD <- 0.03
> p1 <- 0.25
> alpha <- 0.05
> theta <- c(1.35,1.40,1.45)
> beta1 <- 0.8
> s_nb <- c(1463,722,468)
> cat("n","pD","p1","hr","q","power","ssize\n",file=outfile,sep="\t")
> for(i in 1:3)
+ {
+   q <- s_nb[i]/n
+   power <- ccsize(n,q,pD,p1,alpha,log(theta[i]))
+   ssize <- ccsize(n,q,pD,p1,alpha,log(theta[i]),beta1)
+   cat(n,"\t",pD,"\t",p1,"\t",theta[i],"\t",q,"\t",signif(power,3),"\t",ssize,"\n",
+       file=outfile,append=TRUE)
+ }
> read.table(outfile,header=TRUE,sep="\t")

      n   pD   p1   hr          q power ssize
1 15792 0.03 0.25 1.35 0.09264184   0.8  1463
2 15792 0.03 0.25 1.40 0.04571935   0.8   722
3 15792 0.03 0.25 1.45 0.02963526   0.8   468

> unlink(outfile)
> # EPIC study
> outfile <- "epic.txt"
> n <- 25000
```

```
> alpha <- 0.00000005
> power <- 0.8
> s_pD <- c(0.3,0.2,0.1,0.05)
> s_p1 <- seq(0.1,0.5,by=0.1)
> s_hr <- seq(1.1,1.4,by=0.1)
> cat("n","pD","p1","hr","alpha","ssize\n",file=outfile,sep="\t")
> # direct calculation
> for(pD in s_pD)
+ {
+    for(p1 in s_p1)
+    {
+       for(hr in s_hr)
+       {
+          ssize <- ccsize(n,q,pD,p1,alpha,log(hr),power)
+          if (ssize>0) cat(n,"\t",pD,"\t",p1,"\t",hr,"\t",alpha,"\t",ssize,"\n",
+                           file=outfile,append=TRUE)
+       }
+    }
+ }
> read.table(outfile,header=TRUE,sep="\t")

       n  pD  p1  hr alpha ssize
1  25000 0.3 0.1 1.3 5e-08 14391
2  25000 0.3 0.1 1.4 5e-08  5732
3  25000 0.3 0.2 1.2 5e-08 21529
4  25000 0.3 0.2 1.3 5e-08  5099
5  25000 0.3 0.2 1.4 5e-08  2613
6  25000 0.3 0.3 1.2 5e-08 11095
7  25000 0.3 0.3 1.3 5e-08  3490
8  25000 0.3 0.3 1.4 5e-08  1882
9  25000 0.3 0.4 1.2 5e-08  8596
10 25000 0.3 0.4 1.3 5e-08  2934
11 25000 0.3 0.4 1.4 5e-08  1611
12 25000 0.3 0.5 1.2 5e-08  7995
13 25000 0.3 0.5 1.3 5e-08  2786
14 25000 0.3 0.5 1.4 5e-08  1538
15 25000 0.2 0.1 1.4 5e-08  9277
16 25000 0.2 0.2 1.3 5e-08  7725
17 25000 0.2 0.2 1.4 5e-08  3164
18 25000 0.2 0.3 1.3 5e-08  4548
19 25000 0.2 0.3 1.4 5e-08  2152
20 25000 0.2 0.4 1.2 5e-08 20131
21 25000 0.2 0.4 1.3 5e-08  3648
22 25000 0.2 0.4 1.4 5e-08  1805
23 25000 0.2 0.5 1.2 5e-08 17120
24 25000 0.2 0.5 1.3 5e-08  3422
25 25000 0.2 0.5 1.4 5e-08  1713
```

```
26 25000 0.1 0.2 1.4 5e-08  8615
27 25000 0.1 0.3 1.4 5e-08  3776
28 25000 0.1 0.4 1.3 5e-08 13479
29 25000 0.1 0.4 1.4 5e-08  2824
30 25000 0.1 0.5 1.3 5e-08 10837
31 25000 0.1 0.5 1.4 5e-08  2606
```

```
> unlink(outfile)
```

5.4 Graphics examples

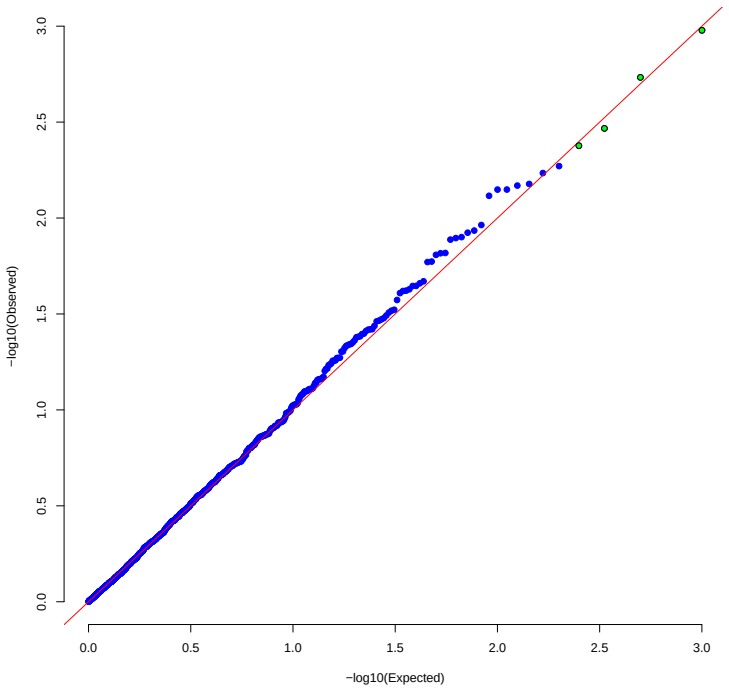
I now include some figures from the documentation that may be of interest.

Genome-wide association

The following code is used to obtain a Q-Q plot via *qqunif* function,

```
> library(gap)
> pdf("figures/qqunif.pdf",height=10,width=10)
> u_obs <- runif(1000)
> r <- qqunif(u_obs,pch=21,bg="blue",bty="n")
> u_exp <- r$y
> hits <- u_exp >= 2.30103
> points(r$x[hits],u_exp[hits],pch=21,bg="green")
> dev.off()

null device
          1
```



Based on a chicken genome scan data, the code below generates a Manhattan plot, demonstrating the use of gaps to separate chromosomes.

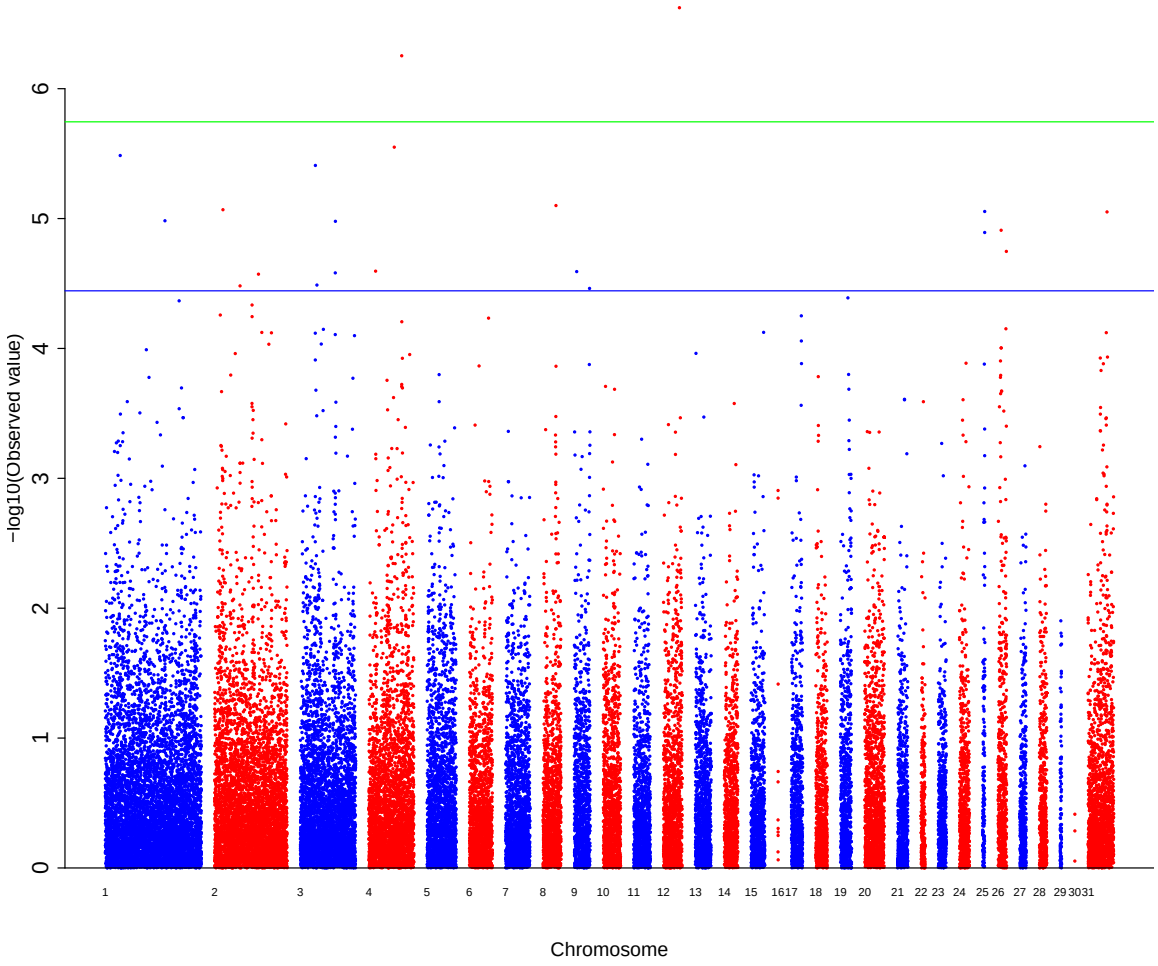
```
> library(gap)
> load("4w.rda")
> ord <- with(d,order(chr,pos))
> d <- d[ord,]
> pdf("figures/4w.pdf",height=9,width=10)
> oldpar <- par()
> par(cex=0.6)
> colors <- c(rep(c("blue","red"),15),"red")
> mhtplot(d,control=mht.control(colors=colors,gap=1000),pch=19,srt=0)

Plotting points  1 - 7244
Plotting points  7245 - 12710
Plotting points  12711 - 16875
Plotting points  16876 - 20271
Plotting points  20272 - 22463
Plotting points  22464 - 24192
Plotting points  24193 - 26021
Plotting points  26022 - 27371
Plotting points  27372 - 28558
Plotting points  28559 - 29860
Plotting points  29861 - 31101
Plotting points  31102 - 32504
Plotting points  32505 - 33690
```

```
Plotting points  33691 - 34708
Plotting points  34709 - 35737
Plotting points  35738 - 35748
Plotting points  35749 - 36594
Plotting points  36595 - 37451
Plotting points  37452 - 38281
Plotting points  38282 - 39765
Plotting points  39766 - 40531
Plotting points  40532 - 40831
Plotting points  40832 - 41432
Plotting points  41433 - 42175
Plotting points  42176 - 42343
Plotting points  42344 - 42983
Plotting points  42984 - 43462
Plotting points  43463 - 44022
Plotting points  44023 - 44131
Plotting points  44132 - 44134
Plotting points  44135 - 46059

> axis(2,cex.axis=2)
> suggestiveline <- -log10(3.60036E-05)
> genomewideline <- -log10(1.8E-06)
> abline(h=suggestiveline, col="blue")
> abline(h=genomewideline, col="green")
> abline(h=0)
> dev.off()

null device
          1
```



The code below obtains a Manhattan plot with gene annotation,

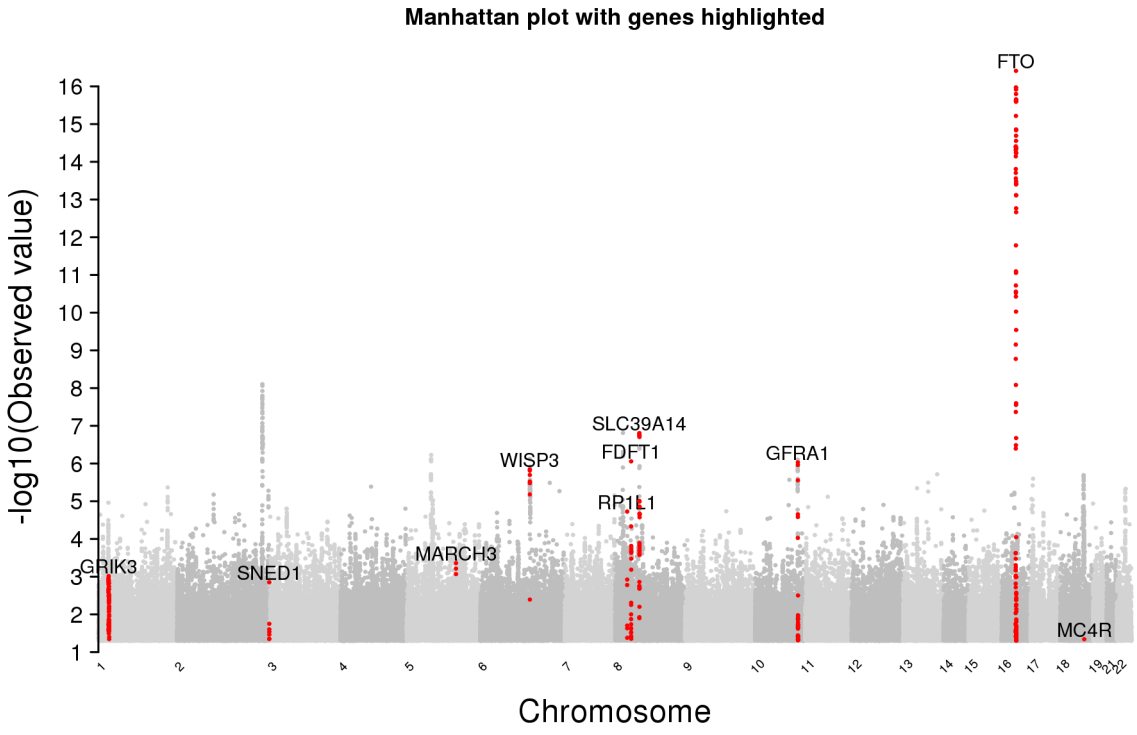
```
> library(gap)
> png("figures/mhtplot.png",height=10,width=16,units="cm",res=300)
> data <- with(mhtdata,cbind(chr,pos,p))
> glist <- c("IRS1","SPRY2","FTO","GRIK3","SNED1","HTR1A","MARCH3","WISP3","PPP1R3B",
+            "RP1L1","FDFT1","SLC39A14","GFRA1","MC4R")
> hdata <- subset(mhtdata,gene%in%glist)[c("chr","pos","p","gene")]
> color <- rep(c("lightgray","gray"),11)
> glen <- length(glist)
> hcolor <- rep("red",glen)
> par(las=2, xpd=TRUE, cex.axis=1.8, cex=0.4)
> ops <- mht.control(colors=color,yline=1.5,xline=3)
> hops <- hmht.control(data=hdata,colors=hcolor)
> mhtplot(data,ops,hops,pch=19)

Plotting points  1 - 12123
Plotting points  12124 - 26444
```

```
Plotting points  26445 - 37326
Plotting points  37327 - 47549
Plotting points  47550 - 58877
Plotting points  58878 - 71908
Plotting points  71909 - 79690
Plotting points  79691 - 90464
Plotting points  90465 - 101267
Plotting points  101268 - 109000
Plotting points  109001 - 116159
Plotting points  116160 - 124094
Plotting points  124095 - 130329
Plotting points  130330 - 134176
Plotting points  134177 - 139300
Plotting points  139301 - 143751
Plotting points  143752 - 148345
Plotting points  148346 - 153379
Plotting points  153380 - 155466
Plotting points  155467 - 157052
Plotting points  157053 - 159312
  ... highlighting 1559 - 1657 GRIK3
  ... highlighting 26343 - 26349 SNED1
  ... highlighting 55142 - 55144 MARCH3
  ... highlighting 66533 - 66539 WISP3
  ... highlighting 81546 - 81551 RP1L1
  ... highlighting 82146 - 82168 FDFT1
  ... highlighting 83425 - 83458 SLC39A14
  ... highlighting 107866 - 107894 GFRA1
  ... highlighting 141457 - 141576 FTO
  ... highlighting 152037 - 152037 MC4R

> axis(2,pos=2,at=1:16)
> title("Manhattan plot with genes highlighted",cex.main=1.8)
> dev.off()

null device
          1
```



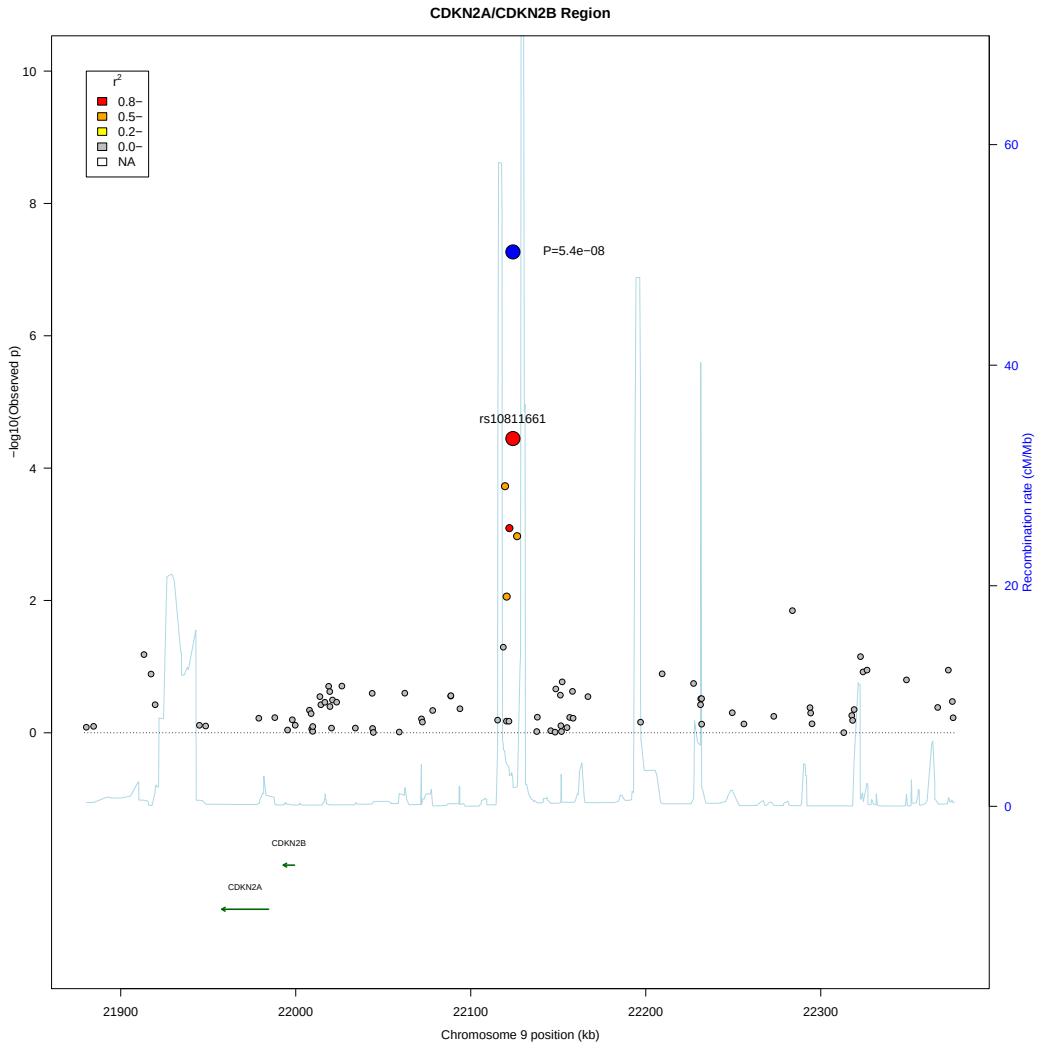
All these look familiar, so revised form of the function called **mhtplot2** was created for additional features such as centering the chromosome ticks, allowing for more sophisticated coloring schemes, using prespecified fonts, etc. Please refer to the function's documentation example.
The code below obtains a regional association plot with the *asplot* function,

```
> library(gap)
> pdf("figures/asplot.pdf",height=14,width=14)
> asplot(CDKNlocus, CDKNmap, CDKNgenes, best.pval=5.4e-8, sf=c(3,6))

- CDKN2A
- CDKN2B

> title("CDKN2A/CDKN2B Region")
> dev.off()

null device
          1
```



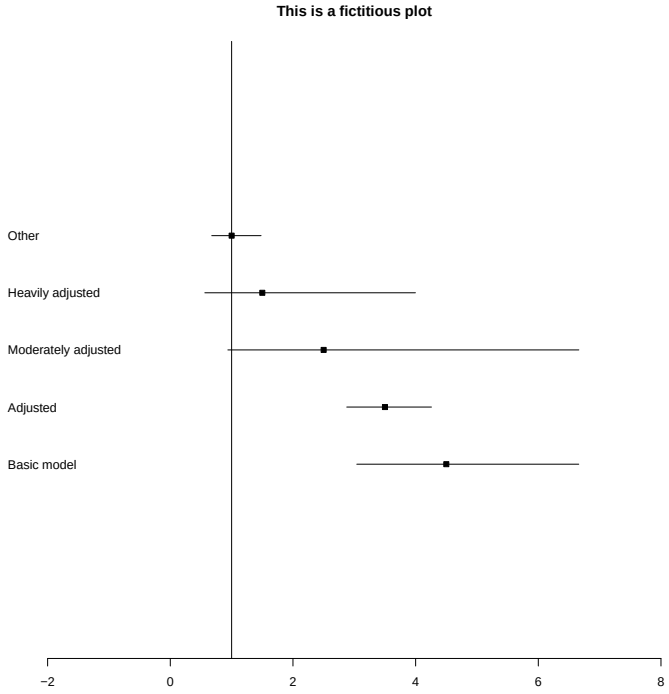
The function predates the currently popular **locuszoom** software but leaves the option open for generating such plots on the fly and locally.

Effect size plot

The code below obtains an effect size plot via the ESplot function.

```
> library(gap)
> pdf("figures/ESplot.pdf",height=10,width=10)
> options(stringsAsFactors=FALSE)
> testdata <- data.frame(models=c("Basic model","Adjusted","Moderately adjusted",
+                         "Heavily adjusted","Other"),
+ OR = c(4.5,3.5,2.5,1.5,1),
+ SElogOR = c(0.2,0.1,0.5,0.5,0.2))
> ESplot(testdata,v=1)
> title("This is a fictitious plot")
> dev.off()
```

```
null device
          1
```



Note that all these can serve as templates to customize features of your own.

6 Polygenic modeling

In line with the recent surge of interest in the polygenic models, a separate vignette is available through `vignette("h2",package="gap")` demonstrating aspect of the models on heritability.

7 Known bugs

Unaware of any bug. However, better memory management is expected.

8 Summary

I believe by now the package should have given you a flavour of initiatives I have made so far in relation to how the project was envisaged. More importantly, it is clear that availability of the package will serve as a platform on which future work can be accumulated and collaboration can be built.

9 Bibliographic note

The main references are Chow (1960); Guo and Thompson (1992); Williams et al. (1992); Gholamic and Thomas (1994); Hartung et al. (2008); Risch and Merikangas (1996); Spielman and Ewens (1996); Risch and Merikangas (1997); Miller (1997); Sham (1997); Elston (1975); Sham (1998); Devlin and Roeder (1999); Zhao et al. (1999); Guo and Lange (2000); Hirotsu et al. (2001); Zhao et al. (2002); Zaykin et al. (2002); Zhao (2004); Wacholder et al. (2004); Wang (2005); Skol et al. (2006); Wakefield (2007).

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